A Phase I, Open-Label, Multicenter, Dose Escalation and Expansion Study of HM16390, as a Single Agent and in Combination with pembrolizumab, in Patients with Advanced or Metastatic Solid Tumors

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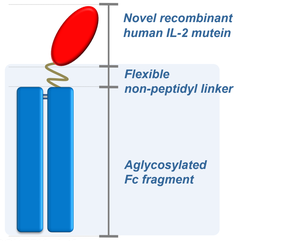
Abstract #539

Background



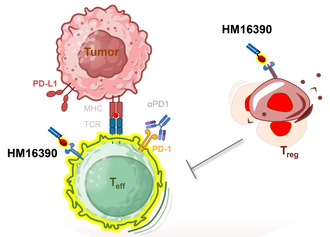
LAPSCOVERY platform:
Long Acting Peptide/Protein DiSCOVERY Technology

Figure 1. Structure of HM16390

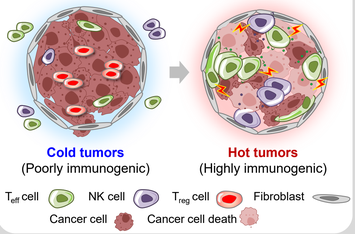
- IL-2 (Interleukin-2), a potent T-cell growth factor, promotes the conversion of immunologically 'cold tumors' into "hot tumors" by modulating the tumor microenvironment (TME). IL-2 enhances tumor infiltrating lymphocytes (TIL), providing a strong rationale for combination partner for immune checkpoint inhibitors (ICIs).
- Several IL-2 analogs have been designed to attenuate CD25 binding affinity to mitigate peripheral toxicities such as vascular leak syndrome (VLS) and cytokine release syndrome (CRS). However, these modifications often compromise CD122-mediated proinflammatory signaling, resulting in diminished antitumor efficacy.
- HM16390 is a novel, long-acting IL-2 analog with beta-intensified affinity and alpha-optimized binding, designed to favor effector T-cell (T_{eff}) expansion over regulatory T cell (T_{reg}) activation. This binding profile induces enhanced tumor infiltration of T_{eff}, while limiting T_{reg} activation and reducing the risk of IL-2–related toxicities.
- HM16390 is fused to a human IgG4 Fc fragment, providing extended half-life and convenient subcutaneous (SC) administration once per treatment cycle.
- Based on promising nonclinical findings, a first-in-human Phase 1 trial of HM16390 has been initiated to assess safety, pharmacokinetics, and preliminary efficacy, both as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors.

Mode of Action

➢ **Favorable binding affinity to IL-2R subunits (Preferential binding to IL-2Rβγ over IL-2Rα)**

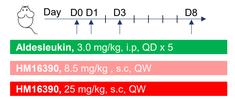


➢ **Enhance tumor infiltration by T_{eff} and reduce T_{reg} activation at tumor microenvironment (TME)**

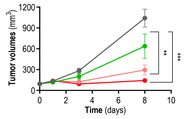


Tumor infiltrating lymphocyte phenotyping of HM16390 in melanoma mouse model

(A) Study design

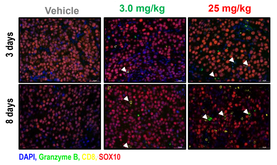


(B) Tumor volume



*p<0.05, **p<0.01, ***p<0.001 vs. vehicle, ANOVA

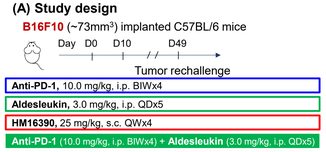
(C) Multiplex IHC in TME



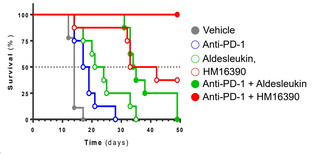
Arrows indicate the co-localization of Granzyme B and CD8 nearby SOX10

Anti-tumor efficacy of HM16390 with Anti-mPD-1 in melanoma mouse model

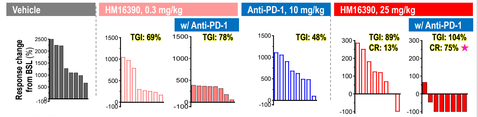
(A) Study design



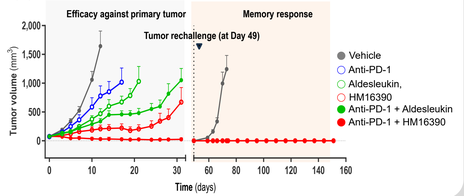
(B) Survival rate



(C) Individual tumor volumes (Day10)



(D) Tumor volume



Study Design

- This is a Phase I, open-label, multicenter study enrolling patients with advanced or metastatic solid tumors (NCT06724016).
- In the monotherapy arm, HM16390 is administered subcutaneously once every 3 weeks (Q3W). In the combination arm, HM16390 is administered subcutaneously and pembrolizumab is administered via intravenous (IV) infusion Q3W.
- In the Dose-Escalation Part, approximately 50 subjects will be enrolled for monotherapy, and maximum of 42 subjects for combination therapy. For the Dose-Ranging Part, and Dose-Expansion Part, approximately 80 and 120 subjects are planned to be enrolled, respectively, across both monotherapy and combination cohorts.

Key Eligibility Criteria

Inclusion	• Standard of Care (SOC) failed / intolerant advanced or metastatic solid tumors • ECOG performance status 0 or 1 • Aged 18 years or older
Exclusion	• No prior IL-2, IL-7, or IL-15 therapy

Study Objectives

Primary	• Evaluate safety and tolerability of HM16390, as a single agent and in combination with pembrolizumab
Secondary	• Determine Maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of HM16390, as a single agent and in combination with pembrolizumab • Characterize the pharmacokinetics (PK) of HM16390, as a single agent and in combination with pembrolizumab • Assess the anti-tumor effect of HM16390, as a single agent and in combination with pembrolizumab
Exploratory	• Assess immunogenicity of HM16390, as a single agent and in combination with pembrolizumab • Assess pharmacodynamics (PD) response to HM16390, as a single agent and in combination with pembrolizumab • Explore relationship between PK, PD variables, safety and efficacy, if available

Dose-Escalation Part

Monotherapy (Arm A)

BOIN Design *N=3~12/cohort*
- Dose level 10: 600 μg/kg
- Dose level 9: 450 μg/kg
- Dose level 8: 300 μg/kg
- Dose level 7: 160 μg/kg
- Dose level 6: 80 μg/kg
- Dose level 5: 40 μg/kg
- Dose level 4: 20 μg/kg

ATD Design *N=1/cohort*
- Dose level 3: 10 μg/kg
- Dose level 2: 3 μg/kg
- Dose level 1: 1 μg/kg

Only if HM16390, as a single agent, is deemed safe and tolerable

Combination therapy (Arm B)

3+3 Design *N=3~6/cohort*
- Dose level 10: 600 μg/kg + pembro
- Dose level 9: 450 μg/kg + pembro
- Dose level 8: 300 μg/kg + pembro
- Dose level 7: 160 μg/kg + pembro
- Dose level 6: 80 μg/kg + pembro
- Dose level 5: 40 μg/kg + pembro
- Dose level 4: 20 μg/kg + pembro

- Pembrolizumab: 200 mg IV Q3W.
- The dose of HM16390 may be adjusted based on emerging safety or relevant clinical data collected from Arm A.

ATD: Accelerated titration design; BOIN: Bayesian optimal interval

Dose-Ranging Part

Monotherapy

1:1 Randomization → Dose level 1 / Dose level 2

Combination therapy

1:1 Randomization → Dose level 1 / Dose level 2

- No. of doses (at least 2 doses) to be randomized will be determined based on a comprehensive review of the results from the Dose-Escalation Part
- n = 20 per arm (dose level)

Dose-Expansion Part

Indication 1, RDE # 1

Indication 2, RDE # 2

- #RDE (Recommended dose for expansion) will be determined based on a comprehensive review of the results from Dose-Escalation/-Ranging Part
- Indication will be selected based on:
  1) *Initial clinical results from Dose-Escalation/ Dose-Ranging Part*
  2) *Prevalence and competitive landscape of the indication*
  3) *Additional pre-clinical results*

Study Status

▲Ongoing study sites

- The first patient was enrolled in December 2024, and as of August 2025, a total of 6 patients have been enrolled across ATD and BOIN cohorts
- HM16390 monotherapy demonstrated a favorable safety profile: no dose-limiting toxicities (DLTs), no treatment-related serious adverse events (SAE), and no treatment-related Grade ≥3 adverse events (AE).
- Enrollment of patients in the HM16390 in combination with pembrolizumab is planned to initiate in 2026.

Acknowledgement

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Reference

1. Choi J, Kim J, Jeong S, Kim Y, Park SH, Bae S, et al. A long-acting and Beta-intensified IL-2 analog, HM16390, alters tumors to an immune favorable environment. *J Immunother Cancer.* 2023;11(Suppl 1):A1153.
2. Jeong S, Kim Y, Byun J, Kim J, Choi J, Bae S, et al. The immune modulation of HM16390 induces potent anti-tumor efficacy. *Cancer Res.* 2024;84(7 Suppl):LB119.
3. Kim J, Choi J, Park SH, Kim Y, Byun J, Shin H, et al. Synergistic tumor clearing effect of HM16390 with checkpoint inhibitors. *J Immunother Cancer.* 2024;12(Suppl 2):A839.

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